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Sustained disease control in transplant-ineligible patients: the role of continuous therapy

Antonio Palumbo^{a,*}, Ruben Niesvizky^b

^a Myeloma Unit, Division of Hematology, University of Turin, Azienda Ospedaliero-Universitaria, San Giovanni Battista di Torino, Turin, Italy, Turin, Italy

^b Myeloma Service, Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell Medical College, New York Presbyterian Hospital-Cornell Medical Center, New York, NY 10021, USA

Abstract

Many patients with multiple myeloma (MM) are elderly (aged >65 years) or unfit, and therefore ineligible for stem-cell transplantation. The novel agents thalidomide, bortezomib, and lenalidomide have shown improved outcomes in these patients. This article discusses the role of continuous therapy in improving patient outcomes and how novel agents with better tolerability profiles could lead to a change in the treatment paradigm. According to the proposed concept, treatment of transplant-ineligible patients with MM should include achievement of high-quality responses with effective induction combination regimens, as well as maintenance of the response with long-term therapy for optimal sustained efficacy.

Keywords

- Continuous;
- Elderly;
- Maintenance;
- Multiple myeloma;
- Newly diagnosed;
- Transplant-ineligible

1. Introduction

Multiple myeloma (MM) is a disease that primarily occurs in older patients. Statistics from the USA show a rise in the incidence of MM from 2.2 per 100,000 people aged <65 years to 30.6 per 100,000 people aged ≥65 years [1]. A survival trend analysis of patients diagnosed with MM from 1997 to 2006 showed that, during this time period, median survival increased from 29.9 months to 44.8 months [2]. Improvements in patient outcomes are largely attributed to better supportive care, increased use of high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT) in eligible patients, and the introduction of the novel agents thalidomide, bortezomib, and lenalidomide 2 and 3.

However, these survival benefits, which were predominantly observed in younger patients, have not been as clear in older patients 2, 3 and 4. A study of survival in unselected patients with MM diagnosed between 1950 and 2005 observed a doubling of median overall survival (OS) in patients aged ≤ 65 years during the period 1995–2005, but no significant improvement in patients aged >65 years at diagnosis [3]. Among patients with newly diagnosed MM (NDMM), median survival rose from 33 months to 60 months for those aged <65 years; however, for older patients median survival increased only marginally from 26 to 32 months [2]. The most recent statistics from the USA indicate that the 5-year relative survival for MM patients aged <65 years is 57%; however, this rate falls to 29% for those aged ≥ 65 years, and to 22% for those aged ≥ 75 years [1]. Others have reported that age is associated with higher International Staging System stage, which is a significant risk factor for early mortality in patients with MM [5].

For the purpose of making treatment decisions, patients with symptomatic NDMM are generally categorized as transplantation-eligible and -ineligible. Criteria that have been used to indicate transplantation ineligibility include age >65 years or >70 years, physical fitness/health, serum creatinine level >2.5 mg/dl, Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or 4, major organ (liver, heart, lung, or kidney) dysfunction, history of thrombosis, and the presence of other serious comorbidities 6 and 7. The International Myeloma Working Group (IMWG) guidelines [6] note that in most countries, with the exception of the USA, patients aged >65 years are not considered for transplantation. Furthermore, no randomized trial has shown a survival advantage for patients aged >65 receiving ASCT. The National Comprehensive Cancer Network (NCCN) guidelines for MM do not specify an age limit for ASCT [7]; however, questions remain regarding the impact of this procedure and the related serious toxicities on quality of life 8 and 9.

For patients for whom ASCT is not an option, the treatment goal is to control disease progression for the purpose of extending OS while maintaining a good quality of life 10 and 11. Historically, patients ineligible for HDT-ASCT were treated with alkylating-based regimens, mainly using melphalan plus prednisone (MP), cyclophosphamide, or dexamethasone resulting in overall response rates (ORR) of 40–50%, complete response (CR) rates of $<5\%$, and a median OS of 3 years 9 and 12.

More recently, the introduction of regimens containing thalidomide, bortezomib, and lenalidomide has been associated with improved outcomes in patients with NDMM or relapsed and refractory MM (RRMM) [13]. However, the ideal duration of therapy has not yet been defined. Most physicians treat patients for 1–2 years, after which treatment is stopped, placing the patient at risk of relapse usually within 1 year following treatment cessation [14]. It has been proposed that continuous therapy can suppress minimal residual disease (MRD) and thus extend the remission duration [15]. This article discusses the role of continuous therapy in improving outcomes in transplantation-ineligible patients and how the availability of novel agents, with better tolerability profiles, could allow for a change in the management of these patients.

2. Novel agents as induction therapy in transplant-ineligible patients

2.1. Thalidomide

The addition of thalidomide to the conventional MP regimen (MPT) has been studied in six phase III randomized controlled trials in older patients with NDMM, and a meta-analysis of these trials, including 1685 patients, was recently reported [16]. The meta-analysis included studies with and without thalidomide maintenance as part of the MPT treatment arm. Across studies, MPT was associated with a significantly longer progression-free survival (PFS; 20.3 months vs 14.9 months

with MP; hazard ratio [HR] = 0.68; $p < 0.0001$). Importantly, MPT was associated with a significant improvement in OS, extending OS by 6.6 months to 39.3 months, and reducing the risk of death by 17% compared with MP ($p = 0.004$). However, the improved efficacy of MPT came at the cost of increased toxicity, including a 2.4-fold increased risk of peripheral neuropathy ($p = 0.02$) and a 6.6-fold increased risk of deep-vein thrombosis ($p < 0.001$) versus MP, as shown in another meta-analysis including five of the six MPT trials [17]. Furthermore, individual studies show that MPT is also associated with an increased rate of treatment discontinuation compared with MP (22–42% vs 6–13%, respectively) [18, 19 and 20]. Based on this high level of clinical evidence, the MPT regimen is established as one of the available standards of care for patients aged >65 years [6].

2.2. Bortezomib

In the original VISTA randomized phase III trial after 16.3 months follow-up, the addition of bortezomib (V) to the MP regimen (VMP) improved median time-to-progression (TTP), and significantly improved survival by 39% ($p = 0.008$) [21]. An updated analysis after a median follow-up period of 36.7 months, showed that the median OS was higher with VMP than with MP (not reached vs 43.1 months, respectively; HR = 0.65; $p < 0.001$) [22]. Peripheral neuropathy (any grade: 44% vs 5%), gastrointestinal adverse events (AEs; grade ≥ 3 : 19% vs 5%), and herpes zoster infection (any grade: 13% vs 4%) were reported more frequently among patients treated with VMP compared with those treated with MP. VMP is given for a total of nine treatment cycles of 6 weeks. VMP is another standard of care in elderly patients [6].

2.3. Lenalidomide

The ECOG E4A03 randomized open-label non-inferiority study compared lenalidomide plus high-dose dexamethasone (40 mg on days 1–4, 9–12, and 17–20 of each 28-day cycle) with lenalidomide plus low-dose dexamethasone (40 mg on days 1, 8, 15, and 22 of each 28-day cycle). After four induction cycles, the patients could decide whether to proceed to ASCT or continue therapy until disease progression [23]. Although lenalidomide plus high-dose dexamethasone was associated with a higher response rate (partial response [PR] or better, 79% vs 68%; $p = 0.008$), OS was shorter (87% vs 96%; $p = 0.0002$) and there were higher rates of AEs (52% vs 35%; $p = 0.0001$) compared with lenalidomide plus low-dose dexamethasone. OS was consistently superior across all age groups, including in patients aged ≥ 75 years [24]. Due to these compelling findings, the trial was stopped and patients receiving high-dose dexamethasone were crossed over to the low-dose arm. Based on its safety and efficacy profile, the International Myeloma Working Group guidelines recommend lenalidomide plus low-dose dexamethasone as the standard of care [6].

3. Novel agents and the optimal duration of treatment in transplant-ineligible patients

Continuous therapy may be able to suppress MRD in patients with CR and to reduce tumor burden in those with PR. This concept was investigated in some early studies using alkylators, steroids, and interferon. Studies with alkylators (melphalan) [25] and/or steroids (e.g., dexamethasone, prednisone) [25, 26 and 27] showed that these agents produced a significantly prolonged PFS, but had no impact on OS. Studies with interferon are controversial, with some studies having shown both a prolonged response duration and improved survival [28, 29 and 30], whereas others have shown longer response durations but no prolonged survival [31, 32 and 33], and a few have shown no long-term benefit [34, 35 and 36]. Furthermore, long-term use of these agents is associated with safety concerns, an increased risk of acute myeloid leukemia (AML) in patients treated with long-term melphalan, potential adverse effects on bone metabolism with steroids such as prednisone, and

high rates of dose reductions and treatment discontinuations with interferon-based therapy 29, 31 and 33. Based on these safety concerns, these agents are considered unsuitable for continuous treatment.

4. Novel agents as continuous therapy

The ideal regimen for continuous therapy must be efficacious, well tolerated, and convenient. Novel agents such as thalidomide, lenalidomide, and bortezomib have demonstrated efficacy when used as induction regimens, and are likely to become the standard of care in this setting. The potential of these agents in continuous therapy has also been investigated, with promising results as discussed in greater detail below (Table 1) 18, 19, 37, 38, 39, 40, 41 and 42.

Table 1. Randomized studies employing continuous therapy, including induction and maintenance regimens, in transplant-ineligible patients with NDMM 18, 19, 37 and 42.

Study	Primary endpoint	Eligibility	Induction	n	Maintenance per design	Duration of maintenance	Median age (y)	CR (%)	VGPR (%)	PR (%)	PFS or EFS (mos)	OS (mos)
Thalidomide												
GIMEMA GISMM2001-A [38]	ORR, PFS	Age >65 y or unable to undergo transplant	MP	164	None		72	3.7	11.0 (≥VGPR)	47.6 (≥PR)	14.5	47.6
			MPT	167	T until progression	9.6 months	72	15.6	29.3 (≥VGPR)	68.9 (≥PR)	21.8	45.0
HOVON 49 [18]	EFS	Age >65 y	MP (≤8 cycles)	168	None		73	8% (CR + VGPR)		NS	9	31
NMSG #12 [19]	OS	Ineligible for HDT, age not specified	MPT (≤8 cycles)	165	T until progression	255 days	72	23% (CR + VGPR)		NS	13	40
			MP	175	None		74.1	4	3	33	14	32
NCT00205751 [39]	PFS, ORR	Not eligible for ASCT	MPT	182	T until progression	236 days ^a	74.6	13	10	34	15	29
			TD (n = 145) or MP (n = 144), (both ≤9 cycles)	64 ^b	IFN ^c	8.3 months	72	11	56 (nCR + VGPR)	19	13.2	51.4
MRC myeloma IX [40]	PFS, OS	Age ≥18 y	Intensive (CTD or CVAD) or non-intensive (MP or CTDA)	64 ^b	IFN-T ^c	13.2 months	71	20	45 (nCR + VGPR)	17	27.7	52.6
				408 ^b	None		64	33.9	19.3	29.0	15	39
Bortezomib GIMEMA-MM-03-05 [41]	PFS	Age ≥65 y or not eligible for ASCT	VMP (≤9 cycles)	257	None		71	24	26	31	27.3	87% (3-y OS rate)
			VMPT (≤9 cycles)	254	VT until progression	NS	71	38	21	30	NR	89% (3-y OS rate)
Lenalidomide MM-015 [37,42]	PFS	Age ≥65 y	MP (≤9 cycles)	154	Placebo until progression		NS	4	12 (≥VGPR)	37	16% 2-y PFS rate	NR
			MPR (≤9 cycles)	152	R until progression	NS	NS	16	32 (≥VGPR)	45	55% 2-y PFS rate	NR

^a For patients living longer than 1 year.

^b Patients that went on to their respective maintenance study.

^c Patients from the TD and MP induction arms were pooled and then were randomized to receive either IFN or IFN-T maintenance.

ASCT, autologous stem-cell transplantation; CR, complete response; CTD, cyclophosphamide, thalidomide, and dexamethasone; CTDA, attenuated CTD; CVAD, cyclophosphamide, vincristine, adriamycin, and dexamethasone; HDT, high-dose therapy; HOVON, Dutch-Belgian Cooperative Trial Group for Hematology Oncology; EFS, event-free survival; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; IFN, interferon-α2b; MP, melphalan plus prednisone; MPR, melphalan, prednisone, and lenalidomide; MPT, MP plus thalidomide; MRC, Medical Research Council; nCR, near CR; NMSG, Nordic Myeloma Study Group; NS, not specified; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R, lenalidomide; TD, thalidomide; T, thalidomide plus dexamethasone; VGPR, very good PR; VMP, bortezomib, melphalan, and prednisone; VMPT, bortezomib, melphalan, prednisone, and thalidomide; VT, bortezomib plus thalidomide.

4.1. Thalidomide

Although most of the studies investigating thalidomide as consolidation/maintenance therapy have followed stem-cell transplantation 15, 43, 44, 45 and 46, a few have assessed the use of continuous thalidomide in transplantation-ineligible patients 18, 19, 40 and 47. However, most of these studies did not investigate the contribution of maintenance therapy to the clinical outcomes.

A study by Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) compared MPT followed by thalidomide maintenance with MP alone without maintenance, in patients aged ≤ 65 years and younger patients unable to undergo transplantation [47]. The addition of thalidomide, administered continuously at a dose of 100 mg/day until disease progression, significantly improved PFS (21.8 months vs 14.5 months for MP; $p = 0.004$) and response rates (at least PR, 68.9% vs 47.6%, respectively; $p = 0.001$), but had no effect on OS (45 months vs 48 months, respectively; $p = 0.79$) after a median follow-up of 38.4 months [38]. The median duration of thalidomide therapy was 9.6 months. Patients in the MPT arm had a statistically significantly higher incidence of grade 3–4 thrombosis/embolic AEs (12% vs 2%), peripheral neuropathy (10% vs 1%), infection (8% vs 0%), and gastrointestinal AEs (6% vs 1%) [47].

A subsequent study by the Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON) group similarly compared MPT followed by thalidomide maintenance therapy (50 mg/d) with MP alone and no maintenance therapy in patients aged >65 years [18]. After a median follow-up of 39 months, the primary endpoint of event-free survival was 13 months for patients treated with MPT compared with 9 months for patients treated with MP ($p < 0.001$). Median OS was 40 months for MPT compared with 31 months for MP ($p = 0.05$). The overall grade 3–4 AEs were more frequent in the MPT group, primarily peripheral neuropathy, leading to a higher rate of discontinuation due to AEs (38%), compared with 7% in the MP group. However, despite the higher incidence of AEs associated with MPT, this did not have an impact on the health-related quality of life, suggesting that MPT may be a better regimen from the patient's perspective [48]. The survival benefit observed with continuous thalidomide was not confirmed by a Norwegian phase III study, which found no significant difference in either PFS or OS with MPT compared with MP [19].

An Austrian-led phase III randomized study compared induction therapy with up to nine cycles of thalidomide plus dexamethasone (TD) versus MP in patients with NDMM not eligible for HDT or ASCT because of age (aged >65 years), presence of significant comorbidities, insufficient stem cell reserve, or patient choice [49]. In the second phase of this study, 128 patients who had achieved at least stable disease were randomized, to maintenance therapy with either interferon α -2b (IFN), or thalidomide (100 mg/day) daily plus IFN (T-IFN) until progression or an inability to tolerate treatment [39]. With a median follow-up of 35 months for the analysis of maintenance therapy, PFS was significantly longer in the T-IFN group compared with the IFN group (27.7 months vs 13.2 months; $p = 0.0068$) [39]; however, OS remained similar (52.6 months vs 51.4 months, respectively; $p = 0.81$). Although hematologic toxicity was comparable in the two maintenance groups, patients on T-IFN had significantly more neuropathy, constipation, skin toxicity, and renal impairment.

The MRC Myeloma IX study was the first study to determine the effect of thalidomide maintenance therapy on survival outcomes. The study randomized a total of 820 patients treated with either a high-dose therapy in an intensive pathway (younger/fitter patients) or a non-intensive induction regimen. Following induction, patients were further randomized to thalidomide maintenance (50 mg/day escalating to 100 mg/day) or no maintenance [40]. After a median follow-up from the start of maintenance of 38 months, there was a significant improvement in PFS with thalidomide maintenance (23 months vs 15 months; HR = 1.45; $p < 0.001$); with effective treatment at relapse,

theoretically, this could translate into a survival benefit [40]. Interestingly, the results were dependent on the baseline interphase fluorescence in situ hybridization (FISH) cytogenetic profile. The improvement in PFS was observed in patients with a favorable FISH profile, defined as the absence of adverse cytogenetic abnormalities and including hyperdiploidy, t(6;14) and t(11;14), and there was a trend toward a late benefit of thalidomide maintenance in OS. In contrast, in patients with adverse FISH profiles, including the presence of t(4;14), t(14;16), t(14;20), 1q+ or 17p-, thalidomide maintenance was associated with similar PFS periods, but worse OS ($p = 0.009$). These data suggest that thalidomide maintenance therapy may select for drug-resistant tumor clones in patients with high-risk cytogenetics, a possibility that requires further study. Of note, Morgan et al. performed a meta-analysis of this and other phase III trials that evaluated the effect of thalidomide maintenance therapy [40]. The meta-analysis found that, although the studies differed significantly in design and patient population, they showed a significantly extended OS ($p = 0.047$). The composite survival curve resulting from the pooled analysis of these trials, including 2456 patients, demonstrated a significant late OS benefit ($p < 0.001$). These data highlight the need for long-term follow-up in maintenance studies to demonstrate the benefits of this therapy on OS [40].

The duration of maintenance therapy across trials, including trials of thalidomide maintenance therapy, was short (range, 7–13.5 months) 18, 19, 39, 40 and 41 with a high rate of discontinuations due to AEs (up to 52% [40]), suggesting that thalidomide may not be suitable for long-term maintenance therapy. Treatment-emergent peripheral neuropathy was the most common reason for not initiating or for stopping maintenance 18, 19 and 40.

4.2. Bortezomib plus thalidomide or as monotherapy

The GIMEMA-MM-03-05 phase III study compared induction with VMP plus thalidomide (VMPT) followed by continuous bortezomib (1.3 mg/m^2) plus thalidomide (50 mg/d) (VT) as maintenance for 2 years or until progression or relapse, versus standard induction with VMP without maintenance therapy [41]. After a median follow-up period of 23.2 months, median PFS was not reached in the VMPT-VT group and was 27.3 months in the VMP group. The intensive treatment approach significantly reduced the risk of progression by 33% ($\text{HR} = 0.67$; $p = 0.002$). There was no difference in OS ($p = 0.77$), but the 3-year survival rates in both groups were 87–88%. A landmark analysis aimed at investigating the effect of maintenance therapy on PFS revealed that VT maintenance reduced the risk of disease progression by 51% ($\text{HR} = 0.49$; $p = 0.0003$) [50]. However, this benefit was not seen in patients aged >75 years. Grade 3–4 AEs were more common among patients treated with VMPT-VT, and included hematologic (38% vs 28%) and cardiac complications (10% vs 5%), as well as thromboembolic events (5% vs 2%). During the VT maintenance treatment, 8% of patients experienced grade 3–4 AEs with few cases of newly occurring peripheral neuropathy (5%) and a low rate of maintenance discontinuation due to AEs, indicating that long-term maintenance treatment with VT is feasible. These results are supported by the findings of a phase III study of bortezomib-based regimens in elderly NDMM patients (GEM05MAS65) [51]. Patients were randomized to VMP or VT plus prednisone (VTP) induction therapy. Patients completing induction were subsequently randomized to bortezomib given in 3-weekly cycles (1.3 mg/m^2 on days 1, 4, 8, and 11) every 3 months, and either prednisone (50 mg every other day) (VP) or thalidomide (50 mg/day) (VT), for up to 3 years. Maintenance treatment with both VP and VT was associated with additional tumor reduction and an approximately 2-fold improvement in CR rate (42%) compared with that after induction (24%). The median PFS for all patients was 31 months (median follow-up 32 months), which compares favorably with the PFS achieved with the VMP regimen in the VISTA trial (24 months) [21]; however, the 3-year OS rates in these studies were comparable (70% vs 68% in VISTA) [22]. Longer follow-up is needed to confirm the impact of bortezomib-based treatment on OS.

The phase IIb UPFRONT study is a community-based open-label study that will evaluate the safety and efficacy of three bortezomib-based induction regimens (bortezomib plus either dexamethasone [VD], thalidomide and dexamethasone [VTD], or melphalan and prednisone [VMP]) followed by bortezomib maintenance [52]. Preliminary data show that all induction regimens have high efficacy, with ORRs of 68%, 78%, and 71% with the VD, VTD, and VMP regimens, respectively. Maintenance monotherapy was well tolerated after these induction regimens, and the ORRs following bortezomib maintenance were 71%, 79%, and 73% for the VD, VTD, and VMP induction regimens, respectively. A quality of life (QoL) analysis from the UPFRONT study showed a decrease in mean global health status at first with all regimens, followed by a trend to stabilizing/improving score during the maintenance phase [53]. Data on survival outcomes are awaited.

4.3. Lenalidomide

The efficacy and safety of lenalidomide in patients with MM was first established in two landmark clinical trials in patients with RRMM (MM-009 and MM-010) [54 and 55]. The trial with Biaxin (clarithromycin), Revlimid (lenalidomide)/dexamethasone (BiRD) combination therapy in patients with treatment-naïve symptomatic MM suggested that continued therapy improved the depth of response [56]. A later retrospective pooled analysis of the two landmark trials [57] demonstrated the benefit of continued lenalidomide therapy: half the patients improved their type of response from a PR to a CR or VGPR with further treatment. The use of a lenalidomide maintenance regimen was investigated in a further prospective, randomized, phase III trial (MM-015) in which elderly NDMM patients received melphalan, prednisone, lenalidomide with lenalidomide maintenance (MPR-R), MPR followed by placebo maintenance (MPR), or MP plus placebo followed by placebo maintenance (MP) [37]. Lenalidomide (10 mg/day, 21 days of a 28-day cycle) was administered until progression. In the primary comparison, MPR-R reduced the risk of progression by 60% compared with MP (HR = 0.40; $p < 0.001$), with a median PFS of 31 months versus 13 months with MP. The incidence of grade 3–4 hematologic AEs was higher with MPR induction versus MP (neutropenia 96% vs 37%; thrombocytopenia 50% vs 16%; and anemia 29% vs 15%). The effect of maintenance treatment on PFS was examined in a landmark analysis comparing the MPR-R and MPR arms for patients who completed induction. This analysis demonstrated that maintenance lenalidomide resulted in a 66% reduced risk of progression compared with no maintenance (HR = 0.34; $p < 0.001$). Lenalidomide maintenance was well tolerated with no evidence of cumulative toxicity and low rates of newly occurring AEs; grade 3–4 hematologic AEs included neutropenia 7%, thrombocytopenia 6%, and anemia 4% [37].

An increase in the incidence of second primary malignancies (SPMs) was observed in the study of lenalidomide maintenance treatment (MM-015). The 3-year risk of an invasive SPM was 7% with MPR-R and 3% with MP [37]. Twelve cases of SPM were reported in the MPR-R arm, nine in the MPR arm and four in the MP arm. These included seven hematologic SPMs in the MPR-R arm (four AML, one acute lymphoblastic leukemia [ALL], one myelodysplastic syndrome [MDS], one chronic myelomonocytic leukemia [CMML]), five in the MPR arm (two AML, three MDS) and one in the MP arm (MDS). There were also five invasive solid tumors in the MPR-R arm, four in the MPR arm and three in the MP arm. No B-cell malignancies were reported. Two other analyses of SPM rates in NDMM patients following lenalidomide treatment have recently been published. An analysis of pooled data from 2459 NDMM patients (median age 69 years) treated with lenalidomide in nine clinical trials carried out by the European Myeloma Network [58] identified a low SPM incidence rate of 0.72 per 100 patient years which included eight hematologic and 22 solid cancers. In addition, analysis of a cohort of patients treated with lenalidomide as first-line therapy in combination with clarithromycin and dexamethasone (BiRD) regimen until disease progression [59] did not identify an increased incidence of SPM and no hematologic SPMs were observed after six

years of follow-up. In conclusion, physicians should bear in mind the risk of SPM when considering continuous lenalidomide treatment and all patients should be evaluated for SPMs using standard cancer screening methods before, and regularly during, lenalidomide treatment. However, the risk of death due to progression of MM remains far higher than the risk of developing a secondary cancer [60] and in the context of the significant gains in PFS associated with lenalidomide maintenance treatment, the risk: benefit profile of continuous lenalidomide treatment remains positive.

4.4. Other induction/consolidation/maintenance regimens

Other induction/consolidation/maintenance approaches are being tested in clinical trials. For example, a recent single-arm phase II study evaluated induction therapy with bortezomib, dexamethasone, and pegylated liposomal doxorubicin (PAD), followed by reduced intensity ASCT (tandem melphalan 100 mg/m² [MEL100] with stem-cell support), and PAD followed by consolidation therapy with lenalidomide (25 mg/day for 21 days of each 28-day cycle) plus prednisone (50 mg every other day) (LP), followed by maintenance therapy with lenalidomide (10 mg/day for 21 days of each 28-day cycle) (LP-Len) until relapse. The study included 102 NDMM patients with a median age of 67 years, 26% of whom were aged >70 years [61]. The immunofixation-negative CR rate increased from 13% after PAD induction, to 38% after MEL100, and 66% after LP-Len consolidation-maintenance. After a median follow-up of 21 months, the 2-year PFS rate was 69% and the 2-year OS was 86%. Lenalidomide consolidation was generally well tolerated with no cumulative hematologic AEs. This interesting sequential approach, evaluating lenalidomide as both consolidation and maintenance, requires testing in a randomized phase III setting. A second, two-stage, phase II trial, investigated the safety and efficacy of lenalidomide plus prednisone (RP) induction therapy followed by MPR consolidation, and lenalidomide maintenance in unfit elderly patients aged >65 years. Response rates at induction were 73% PR or better, and this increased following MPR consolidation (78% achieved PR or better). This treatment regimen was found to have a manageable safety profile with reduced risks of anemia, thrombocytopenia, and non-hematologic events during MPR consolidation in the unfit elderly population [62].

5. Ongoing continuous therapy trials with novel agents

There are several different continuous therapy regimens being tested in ongoing randomized phase III studies in NDMM patients ineligible for transplantation (Fig. 1). Five of these studies investigated lenalidomide-based continuous therapy regimens, and all treated patients until disease progression. One study evaluated lenalidomide alone, one evaluated lenalidomide plus prednisone, and three studies evaluated lenalidomide plus dexamethasone. There are also four studies investigating bortezomib-based continuous therapy regimens. Of interest, two of the bortezomib studies treated patients until disease progression (bortezomib alone and bortezomib plus thalidomide), whereas the others defined “maintenance” as four cycles (cycles 9–13).

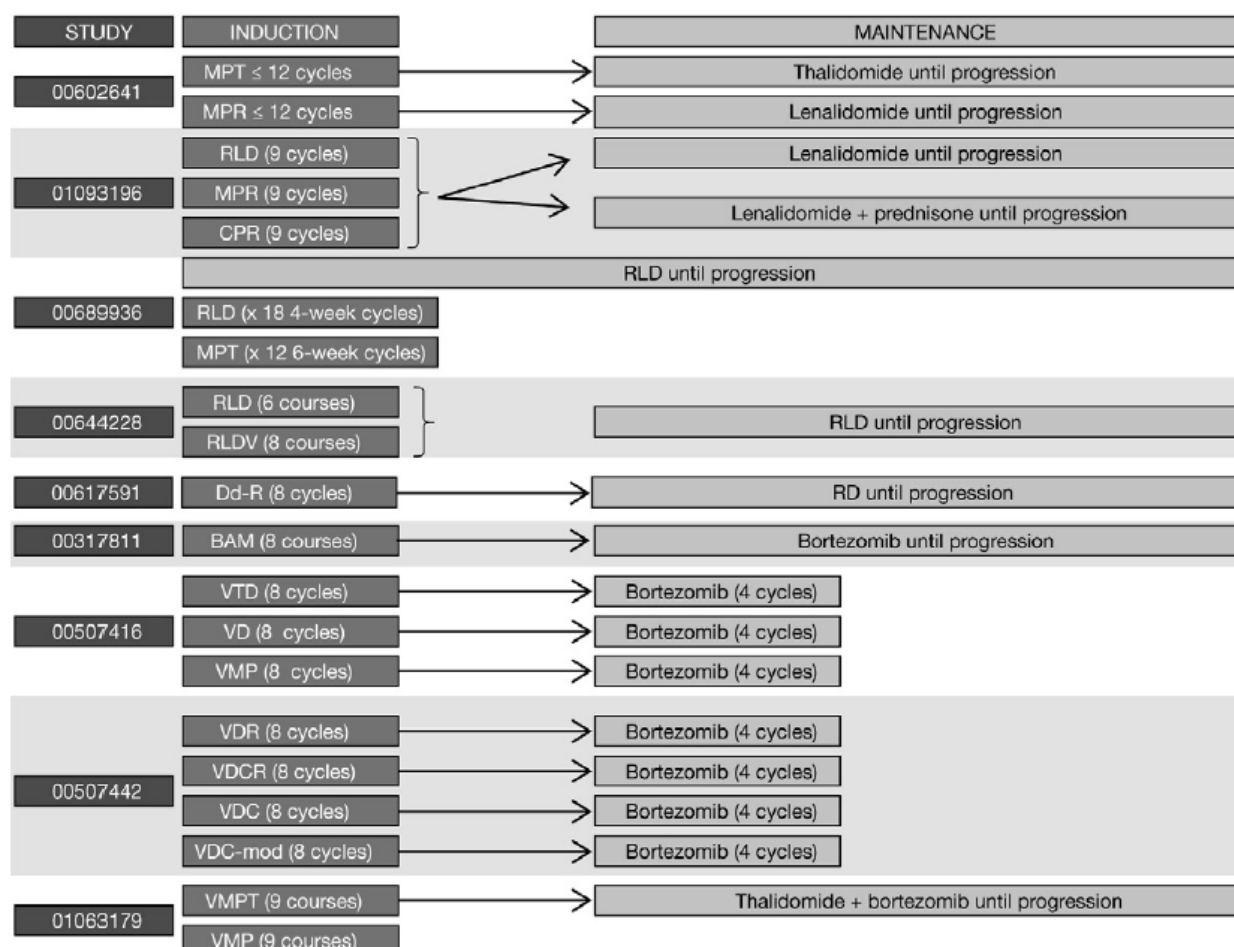


Fig. 1. Schematic of ongoing studies investigating maintenance regimens. BAM, bortezomib, ascorbic acid, and melphalan; CPR, cyclophosphamide, prednisone, and lenalidomide; Dd-R, low frequency dexamethasone and lenalidomide; MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; RD, lenalidomide plus dexamethasone; RLD, lenalidomide plus low-dose dexamethasone; RLDV, lenalidomide, low-dose dexamethasone, and bortezomib; VD, bortezomib and dexamethasone; VDC, bortezomib, dexamethasone, and cyclophosphamide; VDC-mod, modified dosing of VDC; VDCR, bortezomib, dexamethasone, cyclophosphamide, and lenalidomide; VDR, bortezomib, dexamethasone, and lenalidomide; VMP, bortezomib, melphalan, and prednisone; VMPT, VMP plus thalidomide; VTD, bortezomib, thalidomide, and dexamethasone.

6. Challenges in the interpretation of studies investigating continuous therapy

Current evidence from clinical studies of novel agents suggests that although continuous therapy may be associated with a PFS benefit, this benefit does not always translate into an improvement in OS. Furthermore, the studies of continuous therapy published to date have had widely differing study designs and patient populations making comparison between studies difficult. Different induction regimens were used 25, 26, 29 and 31, the length of induction and the duration of follow-up varied, there was heterogeneity in patient characteristics across studies (for example, the cytogenetic profiles of patients) 5, 40 and 63, and type of salvage therapy used at relapse 26, 31 and 41 varied substantially. In addition, interpretation of the results from the maintenance phases

of these studies could be confounded by closer observation of patients in the control (no maintenance) arm.

7. Future perspectives

For transplant-ineligible patients, continuous long-term therapy with novel agents prolongs the TTP and suggests the need for a change in the treatment paradigm. In accordance with this new perspective, treatment for transplant-ineligible MM patients should include: (a) achievement of high-quality responses with effective induction combination regimens including novel agents; and (b) sustainment of the response with maintenance therapy. Although an OS benefit of maintenance therapies is not yet apparent, such a benefit may emerge with longer follow-up periods [64]. Several unanswered questions should be addressed by future research: Should maintenance therapy be administered to all elderly patients with NDMM? Are there any clinical characteristics, such as cytogenetic profile, which would help predict which patients would benefit most from continuous therapy? What type of dosing regimen/schedule is needed to provide optimal disease control while balancing safety and tolerability, considering that the patients are usually elderly and frail? Does continuous therapy result in the development of more aggressive/resistant disease, and if so, in which patients? Should maintenance therapy be given for a limited period (for example, 2–3 years), or continuously until relapse or disease progression? Are there biological markers that can indicate when treatment can be stopped without risk of relapse? What is the optimal subsequent treatment approach in patients relapsing on continuous therapy? More well-designed, comparative studies with longer follow-up periods are needed to answer these questions.

Conflict of interest statement

Dr. Palumbo has had a consultant role for Celgene Corporation and Janssen-Cilag, and received honoraria from Onyx Pharmaceuticals, Bristol-Myers Squibb, Celgene Corporation and Janssen-Cilag. Dr. Niesvizky has acted as a consultant for Millennium, Celgene Corporation and Onyx, and has participated in speaker bureaus for Millennium, Celgene Corporation, and Onyx.

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References

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to SEER website, 2011.

2. SK Kumar, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, et al.

Improved survival in multiple myeloma and the impact of novel therapies

Blood, 111 (5) (2008), pp. 2516–2520

3. I Turesson, R Velez, SY Kristinsson, O Landgren

Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study

J Clin Oncol, 28 (5) (2010), pp. 830–834

4. H Brenner, A Gondos, D Pulte

Recent major improvement in long-term survival of younger patients with multiple myeloma

Blood, 111 (5) (2008), pp. 2521–2526

5. H Ludwig, V Bolejack, J Crowley, J Bladé, JS Miguel, RA Kyle, et al.

Survival and years of life lost in different age cohorts of patients with multiple myeloma

J Clin Oncol, 28 (9) (2010), pp. 1599–1605

6. A Palumbo, O Sezer, R Kyle, JS Miguel, RZ Orlowski, P Moreau, IMWG, et al.

International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation

Leukemia, 23 (10) (2009), pp. 1716–1730

7. National Comprehensive Cancer Network

NCCN clinical practice guidelines in oncology: multiple myeloma, 2010

Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
Accessed December 12, 2011.

8. R Niesvizky, M Coleman, T Mark

Best practices in the management of newly diagnosed multiple myeloma patients who will not undergo transplant

Oncology (Williston Park), 24 (3 Suppl. 2) (2010), pp. 14–21

9. F Morabito, M Gentile, C Mazzone, S Bringhen, E Vigna, E Lucia, et al.

Therapeutic approaches for newly diagnosed multiple myeloma patients in the era of novel drugs

Eur J Haematol, 85 (3) (2010), pp. 181–191

10. BG Durie

Role of new treatment approaches in defining treatment goals in multiple myeloma – the ultimate goal is extended survival

Cancer Treat Rev, 36 (Suppl. 2) (2010), pp. S18–S23

11. SV Rajkumar.

Treatment of myeloma: cure vs control

Mayo Clin Proc, 83 (10) (2008), pp. 1142–1145

12. Myeloma Trialists' Collaborative Group

Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials

J Clin Oncol, 16 (12) (1998), pp. 3832–3842

13. A Palumbo, K Anderson

Multiple myeloma

N Engl J Med, 364 (11) (2011), pp. 1046–1060

14. D Longo, K Anderson

Plasma cell disorders

D Longo, A Fauci, D Kasper, S Hauser, J Jameson, J Loscalzo (Eds.), *Harrison's Principles of Internal Medicine* (16th ed.), MacGraw-Hill Companies Inc., New York (2005), pp. 656–662

15. M Attal, JL Harousseau, S Leyvraz, C Doyen, C Hulin, L Benboubker, Inter-Groupe Francophone du Myélome (IFM), et al.

Maintenance therapy with thalidomide improves survival in patients with multiple myeloma

Blood, 108 (10) (2006), pp. 3289–3294

16. PM Fayers, A Palumbo, C Hulin, A Waage, P Wijermans, M Beksac, Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, European Myeloma Network, et al.

Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Blood, 118 (5) (2011), pp. 1239–1247

17. P Kapoor, SV Rajkumar, A Dispenzieri, MA Gertz, MQ Lacy, D Dingli, et al.

Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis

Leukemia, 25 (4) (2011), pp. 689–696

18. P Wijermans, M Schaafsma, F Termorshuizen, R Ammerlaan, S Wittebol, H Sinnige, Dutch-Belgium Cooperative Group HOVON, et al.

Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study

J Clin Oncol, 28 (19) (2010), pp. 3160–3166

19. A Waage, P Gimsing, P Fayers, N Abildgaard, L Ahlberg, B Björkstrand, K Carlson, Nordic Myeloma Study Group, et al.

Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma

Blood, 116 (9) (2010), pp. 1405–1412

20. C Hulin, T Facon, P Rodon, B Pegourie, L Benboubker, C Doyen, et al.

Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial

J Clin Oncol, 27 (22) (2009), pp. 3664–3670

21. JF San Miguel, R Schlag, NK Khuageva, MA Dimopoulos, O Shpilberg, M Kropff, I Spicka, VISTA Trial Investigators, et al.

Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma
N Engl J Med, 359 (9) (2008), pp. 906–917

22. MV Mateos, PG Richardson, R Schlag, NK Khuageva, MA Dimopoulos, O Shpilberg, et al.

Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial

J Clin Oncol, 28 (13) (2010), pp. 2259–2266

23. SV Rajkumar, S Jacobus, NS Callander, R Fonseca, DH Vesole, ME Williams, Eastern Cooperative Oncology Group, et al.

Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial

Lancet Oncol, 11 (1) (2010), pp. 29–37

24. DH Vesole, S Jacobus, SV Rajkumar, R Abonour, NS Callander, PR Greipp, Eastern Cooperative Oncology Group, et al.

Lenalidomide plus low-dose dexamethasone (Ld): superior one and two year survival regardless of age compared to lenalidomide plus high-dose dexamethasone (LD)

Blood (ASH Annual Meeting Abstracts), 116 (2010) [Abstract 308].

25. A Belch, W Shelley, D Bergsagel, K Wilson, P Klimo, D White, et al.

A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients

Br J Cancer, 57 (1) (1988), pp. 94–99

26. C Shustik, A Belch, S Robinson, SH Rubin, SP Dolan, MJ Kovacs, et al.

A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7

Br J Haematol, 136 (2) (2007), pp. 203–211

27. SE Salmon, JJ Crowley, SP Balcerzak, RW Roach, SA Taylor, SE Rivkin, W Samlowski

Interferon versus interferon plus prednisone remission maintenance therapy for multiple myeloma: a Southwest Oncology Group Study

J Clin Oncol, 16 (3) (1998), pp. 890–896

28. F Mandelli, G Avvisati, S Amadori, M Boccadoro, A Gernone, VM Lauta, et al.

Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy

N Engl J Med, 322 (20) (1990), pp. 1430–1434

29. GP Browman, D Bergsagel, D Sicheri, S O'Reilly, KS Wilson, S Rubin, et al.

Randomized trial of interferon maintenance in multiple myeloma: a study of the National Cancer Institute of Canada Clinical Trials Group

J Clin Oncol, 13 (9) (1995), pp. 2354–2360

30. E Fritz, H Ludwig

Interferon- α treatment in multiple myeloma: Meta-analysis of 30 randomised trials among 3948 patients

Ann Oncol, 11 (11) (2000), pp. 1427–1436

31. J Bladé, JF San Miguel, ML Escudero, M Fontanillas, J Besalduch, S Gardella, et al.

Maintenance treatment with interferon alpha-2b in multiple myeloma: a prospective randomized study from PETHEMA (Program for the Study and Treatment of Hematological Malignancies, Spanish Society of Hematology)

Leukemia, 12 (7) (1998), pp. 1144–1148

33. CG Schaar, HC Kluin-Nelemans, C Te Marvelde, S le Cessie, WP Breed, WE Fibbe, Dutch-Belgian Hemato-Oncology Cooperative Group HOVON, et al.

Interferon-alpha as maintenance therapy in patients with multiple myeloma

Ann Oncol, 16 (4) (2005), pp. 634–639

34. MT Drayson, CE Chapman, JA Dunn, AB Olujohungbe, IC MacLennan

MRC trial of α 2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC Working Party on Leukaemia in Adults

Br J Haematol, 101 (1) (1998), pp. 195–202

35. SE Salmon, JJ Crowley, TM Grogan, P Finley, RP Pugh, B Barlogie

Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma: a Southwest Oncology Group study

J Clin Oncol, 12 (11) (1994), pp. 2405–2414

36. D Peest, H Deicher, R Coldewey, R Leo, R Bartl, H Bartels, et al.

A comparison of polychemotherapy and melphalan/prednisone for primary remission induction, and interferon-alpha for maintenance treatment, in multiple myeloma. A prospective trial of the German Myeloma Treatment Group

Eur J Cancer, 31A (2) (1995), pp. 146–151

37. A Palumbo, R Hajek, M Delforge, M Kropff, MT Petrucci, J Catalano, et al.

Continuous lenalidomide treatment for newly diagnosed multiple myeloma

N Engl J Med, 366 (19) (2012), pp. 1759–1769

38. A Palumbo, S Bringhen, AM Liberati, T Caravita, A Falcone, V Callea, et al.

Oral melphalan, prednisone and thalidomide in elderly patients with multiple myeloma: updated results from a randomised controlled trial

Blood, 112 (8) (2008), pp. 3107–3114

39. H Ludwig, Z Adam, E Tóthová, R Hajek, B Labar, M Egyed, et al.

Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma

Haematologica, 95 (9) (2010), pp. 1548–1554

40. GJ Morgan, WM Gregory, FE Davies, SE Bell, AJ Szubert, JM Brown, et al.

The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis

Blood, 119 (1) (2012), pp. 7–15

41. [41] Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al.

Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for

initial treatment of multiple myeloma: a randomized controlled trial. J Clin

Oncol 2010;28(34):5101–09.

42. Palumbo, A, Dimopoulos M, Delforge M, Hajek R, Kropff M, Petrucci MT, et

al. A phase 3 study to determine the efficacy and safety of lenalidomide

combined with melphalan and prednisone in patients \geq 65 years with newly diagnosed multiple myeloma (NDMM). Haematologica (EHA meeting abstracts) 2010;95(Suppl. 2):[Abstract 566].

43. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, Fassas A, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006;354(10):1021–30.

44. Feyler S, Rawstron A, Jackson G, Snowden JA, Cocks K, Johnson RJ. Thalidomide maintenance following high-dose therapy in multiple myeloma: a UK myeloma forum phase 2 study. Br J Haematol 2007;139(3):429–33.

45. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al.; Dutch-Belgian Hemato-Oncology Group (HOVON). A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood 2010;115(6):1113–20.

46. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009;27(11):1788–93.

47. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, et al.; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone

chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367(9513):825–31.

48. Verelst SGR, Termorshuizen F, Uyl-de Groot CA, Schaafsma MR, Ammerlaan AH, Wittebol S, et al.; Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON). Effect of thalidomide with melphalan and prednisone on healthrelated quality of life (HRQoL) in elderly patients with newly diagnosed multiple myeloma: a prospective analysis in a randomized trial. Ann Hematol 2011;90(12):1427–39.

49. Ludwig H, Hajek R, Tóthová E, Drach J, Adam Z, Labar B, et al. Thalidomidedexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. Blood 2009;113(15):3435–42.

50. Palumbo A, Bringhen S, Cavalli M, Ria R, Offidani M, Patriarca F, et al. Bortezomib, melphalan, prednisone and thalidomide followed by maintenance with bortezomib and thalidomide (VMPT-VT) for initial treatment of elderly multiple myeloma patients: updated follow-up and impact of prognostic factors. Blood (ASH Annual Meeting Abstracts) 2010;116:[Abstract 620].

51. Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly

patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010;11(10):934–41.

52. Niesvizky R, Flinn IW, Rifkin RM, Gabrail NY, Charu V, Clowney B, et al. Phase 3b UPFRONT Study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. *Blood (ASH Annual Meeting Abstracts)* 2010;116:[Abstract 619].

53. Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al., Patient-Reported Quality of Life (QoL) in Elderly, Newly Diagnosed Multiple Myeloma (MM) Patients Receiving Bortezomib-Based Combinations: Results From All Randomized Patients in the Community-Based, Phase 3b UPFRONT Study. *Blood (ASH Annual Meeting Abstracts)* 2011;118:[Abstract 1864].

54. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al.; Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133–42.

55. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al.; Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357(21):2123–32.

56. Niesvizky R, Jayabalan DS, Christos PJ, Furst JR, Naib T, Ely S, et al. BiRD (Biaxin

[clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naïve symptomatic multiple myeloma. *Blood* 2008;111(3):1101–9.

57. Harousseau JL, Dimopoulos MA, Wang M, Corso A, Chen C, Attal M, et al. Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. *Haematologica* 2010;95(10):1738–44.

58. Palumbo A, Larocca A, Zweegman S, Lupparelli G, Sinishcalchi A, Musto P, et al. Second primary malignancies in newly diagnosed multiple myeloma patients treated with lenalidomide: analysis of pooled data in 2459 patients. *Blood (ASH Annual Meeting Abstracts)* 2011;118:[Abstract 996].

59. Rossi AC, Mark TM, Jayabalan D, Christos PJ, Zafar F, Pekle K, et al. Incidence of second primary malignancies (SPM) after 6-years follow-up of continuous lenalidomide in first-line treatment of multiple myeloma (MM). *J Clin Oncol* 2011;29(15):(Suppl. 1):[Abstract 8008].

60. Landgren O, Thomas A, Mailankody S. Myeloma and second primary cancers. *N Engl J Med* 2011;365(23):2241–2.

61. Palumbo A, Gay F, Falco P, Crippa C, Montefusco V, Patriarca F, et al. Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients. *J Clin Oncol* 2010;28(5):800–7.

62. Palumbo A, Falco P, Benevolo G, Rossi D, Carella AM, Guglielmelli T, et al. A multicentre, open label study of oral lenalidomide and prednisone (RP) followed by oral lenalidomide melphalan and prednisone (MPR) and oral lenalidomide maintenance in newly diagnosed elderly multiple myeloma patients. *Blood (ASH Annual Meeting Abstracts)* 2010;116:[Abstract 1940].

63. Barlogie B, Pineda-Roman M, van Rhee F, Haessler J, Anaissie E, Hollmig K, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood* 2008;112(8):3115–21.

64. Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, et al. Longterm follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the Intergroupe Francophone du Myelome, Southwest Oncology Group, and University of Arkansas for Medical Sciences. *J Clin Oncol* 2010;28(7):1209–14.

